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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,499	12/12/2003	Andrei W. Konradi	42837-20027.10	1891

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EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,499	KONRADI ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5 and 7-10* is/are pending in the application.

4a) Of the above claim(s) *7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

As requested in the correspondence from applicants filed 30 October 2006, claims 3,4 and 6 have been cancelled and claims 1, 2, 5, 7 and 8 have been amended. The specification has been amended as well, at page one.

Requirement for Restriction

A Requirement for Restriction of the instant claims to one invention, represented in written form, was mailed to applicants' counsel 26 September 2006. In the Requirement, four inventions were identified, Groups, I, II, III and IV. In reply, applicants indicated election, without traverse, of the invention of Group I, the compounds set forth in the claims wherein the variable "Ar" is a carbocyclic aromatic ring system.

Thus, claims 7-10 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Additionally, in the letter setting forth the Requirement for Restriction, a further requirement was issued for applicants to elect a single disclosed species of whichever invention is elected. An "election of species" requirement, as it were, is customarily understood in cases such as the one at hand to stand for an election of a single *compound* from all of the compounds embraced by the generic embodiment of a claimed invention. The "species" that applicants have identified in response to the election of species requirement is actually a *sub-genus* of the broader genera embodied by instant claims 1 and 2. Because it appears that the election was made in good faith, the sub-genus identified by the applicants as the "elected species" will be accepted as satisfying the

election of species requirement. A compound according to the elected sub-genus is classified in class/subclass 560/133. A pharmaceutical composition comprised thereof, or a medical treatment method wherein the compound is the therapeutic agent is classified in class/subclass 514/490.

The amendment to the claims which limits the scope thereof to the elected subject matter is appreciated.

Because no prior art rendering the "elected species" unpatentable was found, the search of elected Group I was expanded, eventually so as to include the full scope of claims 1 and 2. No prior art rendering a compound according to either independent claim in the instant application was found. Subject matter of Group I is not in condition for allowance, however, for reasons explained in the following pages.

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of the compounds according to formulae I and II, which are specified in claims 1 and 2, respectively, and also for the production of the salts, hydrates and N-oxides thereof does not reasonably provide enablement for the full scope of all 'solvates' of the formulae I and II compounds. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

When making the determination of whether or not a claimed invention is enabled by the accompanying specification, the Office relies upon factors promulgated in the decision rendered in *In re Wands*, which are:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Each of the factors will be addressed with respect to the non-enabled solvates.

(A) Insofar as the solvate embodiment of claims 1, 2 and 5 is concerned, those claims read on solvates of compounds according to formulae I and II, with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug."

(B) The nature of the invention is that of a chemical compound, a pharmaceutical composition or a medical treatment method.

(C), (D), (E) Solvates, at the time the invention was made, were known, but not to such an extent that the preparation of those solvates other than hydrates was routine or simple. The following references address the state of the art with respect to crystalline forms of

organic compounds, formation of solvates of organic compounds, and the predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of formulae I and II is even possible (see Gavezzotti, page 309, point #1).

(F) Aside from a mention that the invention includes solvates (and hydrates) of the compounds, no guidance relevant to preparation of solvates is provided in the disclosure.

(G) No working examples demonstrate the preparation of a solvate. In fact, compounds of the invention are crystallized from a variety of solvents throughout the working examples, yet not solvate of any compound with any of the solvents employed is identified.

(H) Each compound of formulae I and II, of which there are thousands, as a solvate with every solvent within the scope of the term "solvate" generally, of which there are many thousands, represents the efforts of many over a period of years. Those efforts are open-ended and potentially inconclusive. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would be undue. Applicants' right to exclude others from making all solvates of compounds according to formulae I and II is unwarranted in light of the lack of any direction as to how one of ordinary skill would do so.

Deletion of all references to solvates in the claims ("hydrates" need not be deleted) would overcome this rejection.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Also in the definition of R^4 and R^5, the structural elements L^2 and L^3 are not concretely defined. Although the term "a covalent bond," which is recited as one of the alternative identities of L^2 and L^3, is clear and well-defined, the term "a linker atom or group" is not, when read in light of the instant specification. No *specific* definition for the term is set out in the disclosure, and as applicants can surely appreciate, what constitutes a "linker atom or group" in the context of one family of chemical compounds will not be

exactly the same as in another. One of ordinary skill in the chemical arts does not understand the term "linker atom or group" to connote any particular structure, atom or groups thereof. The paragraph bridging pages 8 and 9 of the specification, and the following paragraph on page 9 of the specification only provide some examples of what may meet the limitation "linker atom or group" on the context of the present invention. No clear delineation between what applicants regard as falling within the scope of their invention and what is outside the scope of the inventive subject matter is set out in the specification.

Amendment of the claims so as to incorporate the specific definitions for L^2 and L^3 provided in the specification, *sans* the language "will include" would overcome this ground of rejection. L^2 and L^3 definitions include a variable R^{11}, which must have a corresponding definition included in the claim.

In various definitions of structural elements in formula I and II, "substituted" is recited, in connection with some type of functional group. Although a recitation of "substituted" in connection with some molecular feature, without a list of permitted substituents, is not *per se* indefinite, the term must be clear and well-defined when read in light of the accompanying specification. Definitions for the terms, starting at page 24 of the instant specification, do not make clear exactly what substituents are permitted and what substituents are not, in the context of the present invention. The definitions for "substituted" which are provided in the instant specification are not clear most particularly for the reason that they are "circular" in nature. Every one of the definitions for "substituted" terms includes many recitations of "substituted" itself, so no clear idea of which substituents are contemplated can be ascertained from reading these definitions.

Claim 2, which is an independent claim, does not itself include any definitions for the various elements in the depicted molecular structure diagram. "As defined above" is insufficient for defining terms in an independent claim.

In claims 1 and 5, the variable "R" is defined as "a carboxylic acid or derivative thereof." First, a "carboxylic acid" is contemplative of a chemical compound unto itself, not a functional group within a molecular structure. "A carboxylic acid group" would be more appropriate language. Second, exactly what constitutes a derivative of a carboxylic acid group in the context of the present invention is not clear and well-defined when the claims are read in light of the accompanying specification. Only examples of what might meet the limitation "derivative thereof" with respect to the carboxylic acid group are provided. At page 8, lines 21-23, the instant specification suggests that the term *includes* esters and amides, but does not explicitly exclude any other functional groups. The present claims have been examined as though the definition for "R" were "a carboxylic acid group (-CO_2H) or a derivative thereof selected from lower alkyl ester derivatives, a carboxamide group, or an N-lower alkyl carboxamide group." An amendment incorporating such language into claims 1 and 2 would not be viewed as adding new matter, because the specification is suggestive of these identities for "R," although not limiting "R" to any particular set of functional groups.

Claim 5 is included in this indefiniteness rejection because it depends directly form both claim 1 and claim 2, thereby incorporating all of the limitations of those two claims.

Specification

Objection to the specification, for the reason that the continuity data provided at page one thereof was incomplete, was set forth in the Requirement for Restriction letter.

In view of the amendment to page one of the instant specification, which incorporates reference to the parent application to the instant application, the objection to the specification is hereby withdrawn.

Allowable Subject Matter

Should the outstanding rejections under the first and second paragraphs of 35 U.S.C. 112 be overcome, preferably by amending the claims in the manner suggested hereinabove, the claims of Restriction Group I will be in condition for allowance. At such time, withdrawn claims 7-10 will be eligible for rejoinder. The Requirement for Restriction, as set forth in the 26 September 2006 Office action will be withdrawn upon rejoinder of claims 7-10.

Withdrawn claims 7 and 8 will not present any new patentability issues upon their rejoinder, but claims 9 and 10 will be the subject of a rejection under 35 U.S.C. 112, first paragraph, for lack of a disclosure enabling the practice of the methods specified therein.

At the time the invention was made, the level of ordinary skill in the relevant art was such that only treatment of rheumatoid arthritis (and bone loss diseases like osteoporosis, which are not recited in claims 9 or 10). As evidence, the examiner would rely on the following references, among others:

Miller et al, "Discovery of Orally Active Nonpeptide Vitronectin Receptor Antagonists Based on a 2-Benzazepine Gly-Asp Mimetic" Journal of Medicinal Chemstry, vol. 43, pages 22-26 (2000).

Badger et al, "Disease-Modifying Activity of SB 273005, an Orally Active Nonpeptide αvβ3 (Vltronectin Receptor) Antagonist, in Rat Adjuvant-Induced Arthritis" Arthritis & Rheumatism, vol. 44(1), pages 128-137 (2001).

Lark et al, "Antagonism of the Osteoclast Vitronectin Receptor with an Orally Active Nonpeptide Inhibitor Prevents Cancellous Bone Loss in the Ovarectomized Rat" Journal of Bone and Mineral Research, vol. 16(2), pages 319-327 (2001).

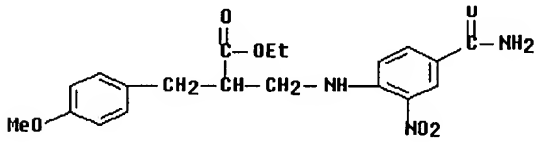
These references are submitted herewith for applicants' review. The full scope of

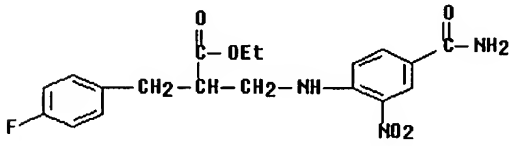
claims 9 and 10, which includes several major diseases for which no particularly effective treatments (*e.g.*, AIDS, tumor metastasis, multiple sclerosis, Alzheimer's disease) have ever been developed, is not enabled by the disclosure.

The closest prior art with respect to compounds according to instant claims 1, 2 and 5 comes from:

> Lee et al, "Solid-Phase Synthesis of 3,4,5-Substituted 1,5-Benzodiazepin-2-ones" Journal of Organic Chemistry, vol. 64, pages 3060-3065 (1999).

which teaches a solid-phase synthesis of certain benzodiazepin-2-one compounds. Intermediates employed in this methodology include two compounds much like those of the present invention. Structures of these compounds are as shown in the following diagrams (the compounds are the fifth and sixth compounds, respectively, disclosed on page 3064):





Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

ZACHARY C. TUCKER
PRIMARY EXAMINER